Claims

1. A method for the identification of a nucleic acid molecule differentially expressed in an *in vitro* model of a biological system, comprising the steps of:

(1) harvesting cells from the model system at predetermined time points;

(2) obtaining total RNA from the cells harvested at each time point;

(3) preparing cDNA from the total RNA from each time point to provide a plurality of pools of cDNA;

(4) performing a suppression subtractive hybridization (SSH) on the cDNA pools from each time point sequentially so as to progressively amplify cDNAs derived from nucleic acid molecules differentially expressed from one time period to the next.

2. A method as claimed in claim 1 wherein the model system is an *in vitro* model for angiogenesis.

3. A nucleic acid molecule differentially expressed during angiogenesis when identified by the method of claim 1 or claim 2.

4. A nucleic acid molecule as claimed in claim 3 selected from the group consisting of those laid out in Tables 1 and 2.

5. A method for the identification of a nucleic acid molecule up-regulated in an *in vitro* model of a biological system, comprising the steps of:

(1) harvesting cells from the model system at predetermined time points;

(2) obtaining total RNA from the cells harvested at each time point;

(3) preparing cDNA from the total RNA from each time point to provide a plurality of pools of cDNA;

(4) performing a suppression subtractive

hybridization (SSH) on the cDNA pools from each time point sequentially so as to progressively amplify cDNAs derived from nucleic acid molecules differentially expressed from one time period to the next.

(5) cloning the amplified cDNAs;

(6) locating DNA from each clone on a microarray;

(7) generating antisense RNA by reverse transcription of total RNA from cells harvested from the *in vitro* model at said predetermined time intervals and labelling the antisense RNA; and

(8) probing the microarray with labelled antisense RNA from 0 hours and each of the other time points separately to identify clones containing cDNA derived from nucleic acid molecules which are up-regulated at said time points in the *in vitro* model.

6. A method as claimed in claim 5 wherein the *in vitro* model is an *in vitro* model for angiogenesis.

7. A nucleic acid molecule when identified by the method of claim 5 or claim 6.

8. A nucleic acid molecule as claimed in claim 7 selected from the group consisting of those set forth in Tables 1 and 2.

9. A polypeptide encoded by a nucleic acid molecule as claimed in any one of claims 3, 4, 7 or 8.

10. An isolated nucleic acid molecule comprising the sequence set forth in one of SEQ ID Numbers: 1 to 44.

11. An isolated nucleic acid molecule comprising the sequence set forth in one of SEQ ID Numbers: 1 to 44 or as laid out in Tables 1 and 2, or a fragment thereof, and

which encodes a polypeptide that plays a role in an angiogenic process.

12. An isolated nucleic acid molecule that is at least 70% identical to a nucleic acid molecule comprising the sequence set forth in one of SEQ ID Numbers: 1 to 44 or as laid out in Tables 1 and 2, and which encodes a polypeptide that plays a role in an angiogenic process.

13. An isolated nucleic acid molecule as claimed in claim 12 that is at least 85% identical.

14. An isolated nucleic acid molecule as claimed in claim 12 that is at least 95% identical.

15. An isolated nucleic acid molecule that encodes a polypeptide that plays a role in an angiogenic process, and which hybridizes under stringent conditions with a nucleic acid molecule comprising the nucleotide sequence set forth in one of SEQ ID Numbers: 1 to 44 or as laid out in Tables 1 and 2.

16. An isolated nucleic acid molecule as claimed in any one of claims 10 to 15, which encodes a polypeptide that plays a role in diseases associated with angiogenesis including but not restricted to cancer, rheumatoid arthritis, diabetic retinopathy, psoriasis, cardiovascular diseases such as atherosclerosis, ischaemic limb disease and coronary artery disease.

17. An isolated nucleic acid molecule consisting any one of the nucleotide sequences set forth in SEQ ID Numbers: 1 to 44.

18. Use of a nucleic acid molecule selected from the group consisting of DNA molecules having the sequence set forth in SEQ ID Numbers: 1 to 15, 17 to 37, and 39 to 44

to identify and/or obtain full-length human genes involved in an angiogenic process.

19. Use as claimed in claim 18 wherein additional sequence is obtained using hybridization with one or more of said nucleic acid molecules, inverse PCR, restriction site PCR, PCR walking techniques or RACE.

20. A gene when identified by the use of a nucleic acid molecule selected from any one of SEQ ID Numbers: 1 to 15, 17 to 37, and 39 to 44.

21. An isolated polypeptide comprising the sequence set forth in one of SEQ ID Numbers: 51 to 58.

22. An isolated polypeptide comprising the sequence set forth in one of SEQ ID Numbers: 51 to 58 or as laid out in Tables 1 and 2, or a fragment thereof, that plays a role in an angiogenic process.

23. An isolated polypeptide that plays a role in an angiogenic process, and having at least 70% identity with the amino acid sequence set forth in SEQ ID Numbers: 51 to 58 or a gene as laid out in Tables 1 and 2.

24. An isolated polypeptide as claimed in claim 23 with at least 85% sequence identity.

25. An isolated polypeptide as claimed in claim 23 with at least 95% sequence identity.

26. An isolated polypeptide as claimed in any one of claims 21 to 25 that plays a role in diseases associated with an angiogenic process including but not restricted to cancer, rheumatoid arthritis, diabetic retinopathy, psoriasis, cardiovascular diseases such as

atherosclerosis, ischaemic limb disease and coronary artery disease.

27. An isolated polypeptide consisting any one of the amino acid sequences set forth in SEQ ID Numbers: 51 to 58.

28. An expression vector comprising a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

29. A cell comprising an expression vector of claim 28.

30. A cell as claimed in claim 29 which is an eukaryotic cell.

31. A method of preparing a polypeptide comprising the steps of :

(1) culturing cells as claimed in either one of claims 29 or 30 under conditions effective for polypeptide production; and

(2) harvesting the polypeptide.

32. A polypeptide prepared by the method of claim 31.

33. A method of modulating angiogenesis comprising modulating the expression or activity of a polypeptide in a cell, wherein the polypeptide is encoded by a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

34. The method of claim 33 wherein the nucleic acid molecule is selected from the group consisting of SEQ ID Numbers: 1 to 44.

35. The method of claim 33 wherein the polypeptide is that which is claimed in any one of claim 9, claims 21 to 27, or claim 32, or an active fragment thereof.

36. The method of claim 35 wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID Numbers: 51 to 58.

37. The method of claim 33 wherein the expression or activity of the polypeptide is modulated by introducing into the cell an antagonist or agonist of a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17, or a polypeptide as claimed in any one of claim 9, claims 21 to 27, or claim 32.

38. The method of claim 33 wherein the expression or activity of the polypeptide is modulated by introducing into the cell an antisense to a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

39. The method of claim 33 wherein the expression or activity of the polypeptide is modulated by introducing into the cell a nucleic acid molecule which is the complement of at least a portion of a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17 and is capable of modulating expression or levels of the nucleic acid molecule.

40. The method of claim 39 wherein the nucleic acid molecule is an RNA molecule that hybridizes with the mRNA encoded by a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

41. The method of claim 39 wherein the nucleic acid molecule is a short interfering oligonucleotide that hybridizes with the mRNA encoded by a nucleic acid

molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

42. The method of claim 39 wherein the nucleic acid molecule is a catalytic nucleic acid molecule that is targeted to a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

43. The method of claim 42 wherein the catalytic nucleic acid molecule is a DNAzyme.

44. The method of claim 42 wherein the catalytic nucleic acid molecule is a ribozyme.

45. The method of claim 33 wherein the polypeptide expression or activity is modulated by an antibody capable of binding the polypeptide.

46. The method of claim 45 wherein the antibody is a fully human antibody.

47. The method of claim 45 wherein the antibody is selected from the group consisting of a monoclonal antibody, a humanised antibody, a chimaeric antibody or an antibody fragment including a Fab fragment, $(Fab')_2$ fragment, Fv fragment, single chain antibodies and single domain antibodies.

48. The method of claim 33 wherein the polypeptide expression or activity is modulated by introducing into the cell a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17, or an active fragment or variant thereof.

49. The method of claim 48 wherein the nucleic acid molecule is introduced by way of an expression vector as claimed in claim 28.

50. The method of claim 33 wherein the polypeptide expression or activity is modulated by introducing into the cell a polypeptide as claimed in any one of claim 9, claims 21 to 27, or claim 32.

51. The method of any one of claims 33 to 50 wherein angiogenesis is uncontrolled or enhanced.

52. The method of any one of claims 33 to 50 wherein angiogenesis is inappropriately arrested or decreased.

53. A method for the treatment of an angiogenesis-related disorder, comprising modulating the expression or activity of a polypeptide encoded by a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

54. The method of claim 53 wherein the nucleic acid molecule is selected from the group consisting of SEQ ID Numbers: 1 to 44.

55. The method of claim 53 wherein the polypeptide is that which is claimed in any one of claim 9, claims 21 to 27, or claim 32, or an active fragment thereof.

56. The method of claim 55 wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID Numbers: 51 to 58.

57. The method of claim 53 wherein the expression or activity of the polypeptide is modulated by introducing into the cell an antagonist or agonist of a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17 or an antagonist or agonist of a polypeptide as claimed in any one of claim 9, claims 21 to 27, or claim 32.

58. The method of claim 53 wherein the expression or activity of the polypeptide is modulated by introducing into the cell an antisense to a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

59. The method of claim 53 wherein the expression or activity of the polypeptide is modulated by introducing into the cell a nucleic acid molecule which is the complement of at least a portion of a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17 and is capable of modulating expression or levels of the nucleic acid molecule.

60. The method of claim 59 wherein the nucleic acid molecule is an RNA molecule that hybridizes with the mRNA encoded by a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

61. The method of claim 59 wherein the nucleic acid molecule is a short interfering oligonucleotide that hybridizes with the mRNA encoded by a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

62. The method of claim 59 wherein the nucleic acid molecule is a catalytic nucleic acid molecule that is targeted to a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

63. The method of claim 62 wherein the catalytic nucleic acid molecule is a DNAzyme.

64. The method of claim 62 wherein the catalytic nucleic acid molecule is a ribozyme.

65. The method of claim 53 wherein the polypeptide expression or activity is modulated by an antibody capable of binding the polypeptide.

66. The method of claim 65 wherein the antibody is a full human antibody.

67. The method of claim 65 wherein the antibody is selected from the group consisting of a monoclonal antibody, a humanised antibody, a chimaeric antibody or an antibody fragment including a Fab fragment, $(Fab')_2$ fragment, Fv fragment, single chain antibodies and single domain antibodies.

68. The method of claim 53 wherein the polypeptide expression or activity is modulated by introducing into the cell a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17, or an active fragment or variant thereof.

69. The method of claim 68 wherein the nucleic acid molecule is introduced by way of an expression vector as claimed in claim 28.

70. The method of claim 53 wherein the polypeptide expression or activity is modulated by introducing into the cell a polypeptide as claimed in any one of claim 9, claims 21 to 27, or claim 32.

71. The method of any one of claims 53 to 70 wherein the angiogenesis-related disorder involves uncontrolled or enhanced angiogenesisis, or is a disorder in which a decreased vasculature is of benefit.

72. The method of claim 71 wherein the disorder is selected from the group consisting of cancer, rheumatoid

arthritis, diabetic retinopathy, psoriasis and cardiovascular diseases such as atherosclerosis.

73. The method of any one of claims 53 to 70 wherein the angiogenesis-related disorder involves inappropriately arrested or decreased angiogenesisis, or is a disorder in which an expanding vasculature is of benefit.

74. The method of claim 73 wherein the disorder is selected from the group consisting of ischaemic limb disease or coronary artery disease.

75. Use of a modulator of expression or activity of a polypeptide encoded by a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17 in the manufacture of a medicament for the treatment of an angiogenesis-related disorder.

76. The use of claim 75 wherein the nucleic acid sequence is selected from the group consisting of SEQ ID Numbers: 1 to 44.

77. The use of claim 75 wherein the polypeptide is that which is claimed in any one of claim 9, claims 21 to 27, or claim 32, or an active fragment thereof.

78. The use of claim 77 wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID Numbers: 51 to 58.

79. The use of claim 75 wherein the expression or activity of the polypeptide is modulated by introducing into the cell an antagonist or agonist of a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17 or an antagonist or agonist of a polypeptide as claimed in any one of claim 9, claims 21 to 27 or claim 32.

80. The use of claim 75 wherein the expression or activity of the polypeptide is modulated by introducing into the cell an antisense to a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

81. The use of claim 75 wherein the expression or activity of the polypeptide is modulated by introducing into the cell a nucleic acid molecule which is the complement of at least a portion of a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17 and is capable of modulating expression or levels of the nucleic acid molecule.

82. The use of claim 81 wherein the nucleic acid molecule is an RNA molecule that hybridizes with the mRNA encoded by a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

83. The use of claim 81 wherein the nucleic acid molecule is a short interfering oligonucleotide that hybridizes with the mRNA encoded by a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

84. The use of claim 81 wherein the nucleic acid molecule is a catalytic nucleic acid molecule that is targeted to a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

85. The use of claim 84 wherein the catalytic nucleic acid molecule is a DNAzyme.

86. The use of claim 84 wherein the catalytic nucleic acid molecule is a ribozyme.

87. The use of claim 75 wherein the polypeptide expression or activity is modulated by an antibody capable of binding the polypeptide.

88. The use of claim 87 wherein the antibody is a full human antibody.

89. The use of claim 87 wherein the antibody is selected from the group consisting of a monoclonal antibody, a humanised antibody, a chimaeric antibody or an antibody fragment including a Fab fragment, $(Fab')_2$ fragment, Fv fragment, single chain antibodies and single domain antibodies.

90. The use of claim 75 wherein the polypeptide expression or activity is modulated by introducing into the cell a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17, or an active fragment or variant thereof.

91. The use of claim 90 wherein the nucleic acid molecule is introduced by way of an expression vector as claimed in claim 28.

92. The use of claim 75 wherein the polypeptide expression or activity is modulated by introducing into the cell a polypeptide as claimed in any one of claim 9, claims 21 to 27, or claim 32.

93. The use of any one of claims 75 to 92 wherein the angiogenesis-related disorder involves uncontrolled or enhanced angiogenesisis, or is a disorder in which a decreased vasculature is of benefit.

94. The use of claim 93 wherein the disorder is selected from the group consisting of cancer, rheumatoid arthritis,

diabetic retinopathy, psoriasis and cardiovascular diseases such as atherosclerosis.

95. The use of any one of claims 75 to 92 wherein the angiogenesis-related disorder involves inappropriately arrested or decreased angiogenesisis, or is a disorder in which an expanding vasculature is of benefit.

96. The use of claim 95 wherein the disorder is selected from the group consisting of ischaemic limb disease or coronary artery disease.

97. The use of a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17 for the screening of candidate pharmaceutical compounds useful in the treatment of angiogenesis-related disorders.

98. A compound useful in the treatment of angiogenesis-related disorders when identified by the use of a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

99. The use of a polypeptide as claimed in any one of claim 9, claims 21 to 27, or claim 32 for the screening of candidate pharmaceutical compounds useful in the treatment of angiogenesis-related disorders.

100. A compound useful in the treatment of angiogenesis-related disorders when identified by the use of a polypeptide as claimed in any one of claim 9, claims 21 to 27, or claim 32.

101. The use of a cell as claimed in either one of claims 29 or 30 for the screening of candidate pharmaceutical compounds useful in the treatment of angiogenesis-related disorders.

102. A compound useful in the treatment of angiogenesis-related disorders when identified by the use of a cell as claimed in either one of claims 29 or 30.

103. A method of screening for a candidate pharmaceutical compound useful in the treatment of angiogenesis-related disorders comprising the steps of:

(1) providing a polypeptide as claimed in any one of claim 9, claims 21 to 27, or claim 32;

(2) adding a candidate pharmaceutical compound to said polypeptide; and

(3) determining the binding of said candidate compound to said polypeptide;

wherein a compound that binds to the polypeptide is a candidate pharmaceutical compound.

104. A method of screening for candidate pharmaceutical compound useful in the treatment of angiogenesis-related disorders comprising the steps of:

(1) providing a cell, as claimed in either one of claims 29 or 30;

(2) adding a candidate pharmaceutical compound to said cell; and

(3) determining the effect of said candidate pharmaceutical compound on the functional properties of said cell;

wherein a compound that alters the functional properties of said cell is a candidate pharmaceutical compound.

105. A method of screening for a candidate pharmaceutical compound useful in the treatment of angiogenesis-related disorders comprising the steps of:

(1) providing a cell, as claimed in either one of claims 29 or 30;

(2) adding a candidate pharmaceutical compound to said cell; and

(3) determining the effect of said candidate pharmaceutical compound on the expression of the nucleic acid molecule that is part of the expression vector in said cell;

wherein a compound that alters the expression of the nucleic acid molecule that is part of the expression vector in said cell is a candidate pharmaceutical compound.

106. A method of screening for a candidate pharmaceutical compound useful in the treatment of angiogenesis-related disorders comprising the steps of:

(1) providing a cell, as claimed in either one of claims 29 or 30;

(2) adding a candidate pharmaceutical compound to said cell; and

(3) determining the effect of said candidate pharmaceutical compound on the expression or activity of the polypeptide encoded by the nucleic acid molecule that is part of the expression vector in said cell;

wherein a compound that alters the expression or activity of polypeptide encoded by the nucleic acid molecule that is part of the expression vector in said cell is a candidate pharmaceutical compound.

107. A compound when identified by the method of any one of claims 103 to 106.

108. A pharmaceutical composition comprising a compound as claimed in any one of claims 98, 100, 102 or 107 and a pharmaceutically acceptable carrier.

109. An antibody which is immunologically reactive with an isolated polypeptide as claimed in claim 21.

110. An antibody as claimed in claim 109 which is a fully human antibody.

111. An antibody as claimed in claim 109 which is selected from the group consisting of a monoclonal antibody, a humanised antibody, a chimaeric antibody or an antibody fragment including a Fab fragment, $(Fab')_2$ fragment, Fv fragment, single chain antibodies and single domain antibodies.

112. A short interfering oligonucleotide targeted to the mRNA encoded by a nucleic acid molecule as claimed in claim 10.

113. A catalytic nucleic acid molecule targeted to a nucleic acid molecule as claimed in claim 10.

114. A catalytic nucleic acid molecule of claim 113 which is a DNAzyme.

115. A catalytic nucleic acid molecule of claim 113 which is a ribozyme.

116. Use of a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17 in the diagnosis or prognosis of an angiogenesis-related disorder.

117. Use of a polypeptide as claimed in any one of claim 9, claims 21 to 27, or claim 32 in the diagnosis or prognosis of an angiogenesis-related disorder.

118. Use of an antibody as claimed in any one of claims 109 to 111 or an antibody to a polypeptide as claimed in any one of claim 9, claims 21 to 27, or claim 32 in the diagnosis or prognosis of an angiogenesis-related disorder.

119. A method for the diagnosis or prognosis of an angiogenesis-related disorder comprising the steps of:

(1) establishing a profile for normal expression and/or activity of a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17, in unaffected subjects;

(2) measuring the level of expression and/or activity of said nucleic acid molecule in a person suspected of abnormal expression and/or activity of the gene; and

(3) comparing the measured level of expression and/or activity of said nucleic acid molecule with the profile for normal expression and/or activity;

wherein an altered level of expression and/or activity of said nucleic acid molecule in said subject is an indication of an angiogenesis-related disorder, or a predisposition thereto.

120. A method as claimed in claim 119 wherein reverse transcriptase PCR is employed to measure levels of expression.

121. A method as claimed in claim 119 wherein a hybridization assay using a probe derived from the gene, or a fragment thereof, is employed to measure levels of expression.

122. A method for the diagnosis or prognosis of an angiogenesis-related comprising the steps of:

(1) obtaining DNA from a subject corresponding to a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17; and

(2) comparing the DNA from said subject to the DNA of the corresponding wild-type nucleic acid molecule;

wherein altered DNA properties in said subject is an indication of an angiogenesis-related disorder, or a predisposition thereto.

123. A method as claimed in claim 122 wherein the DNA of the nucleic acid molecule is sequenced and the sequences compared.

124. A method as claimed in claim 122 wherein the DNA of the nucleic acid molecule is subjected to SSCP analysis.

125. A method for the diagnosis or prognosis of an angiogenesis-related disorder comprising the steps of:

(1) establishing a physical property of a wild-type polypeptide as claimed in any one of claim 9, claims 21 to 27, or claim 32;

(2) obtaining the polypeptide from a person suspected of an abnormality of that polypeptide; and;

(3) measuring the property for the polypeptide expressed by said person and comparing it to the established property for the wild-type polypeptide;

wherein altered polypeptide properties in said subject is an indication of an angiogenesis-related disorder, or a predisposition thereto.

126. A method as claimed in claim 125 wherein the property is the electrophoretic mobility.

127. A method as claimed in claim 125 wherein the property is the proteolytic cleavage pattern.

128. A genetically modified non-human animal comprising a isolated a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

129. A genetically modified non-human animal comprising a disruption of a nucleic acid molecule as claimed in any one of claims 3 to 4, claims 7 to 8, or claims 10 to 17.

130. A genetically modified non-human animal as claimed in either one of claims 128 or 129 in which the animal is selected from the group consisting of rats, mice, hamsters, guinea pigs, rabbits, dogs, cats, goats, sheep, pigs and non-human primates such as monkeys and chimpanzees.

131. A genetically modified non-human animal as claimed in any one of claims 128 to 130 wherein the animal is a mouse.

132. Use of a genetically modified non-human animal as claimed in any one of claims 128 to 131 in screening for candidate pharmaceutical compounds useful for the treatment of angiogenesis-related disorders.

133. The use of any one of claims 97 to 102 or claim 132 wherein the angiogenesis-related disorder involves uncontrolled or enhanced angiogenesis, or is a disorder in which a decreased vasculature is of benefit.

134. The use of claim 133 wherein the disorder is selected from the group consisting of cancer, rheumatoid arthritis, diabetic retinopathy, psoriasis and cardiovascular diseases such as atherosclerosis.

135. The use of any one of claims 97 to 102 or claim 132 wherein the angiogenesis-related disorder involves inappropriately arrested or decreased angiogenesis, or is

a disorder in which an expanding vasculature is of benefit.

136. The use of claim 135 wherein the disorder is selected from the group consisting of ischaemic limb disease or coronary artery disease.